Low-Dose Extrapolation of Radiation-Related Risk

Epidemiological Overview and Quantitative Uncertainty Analysis

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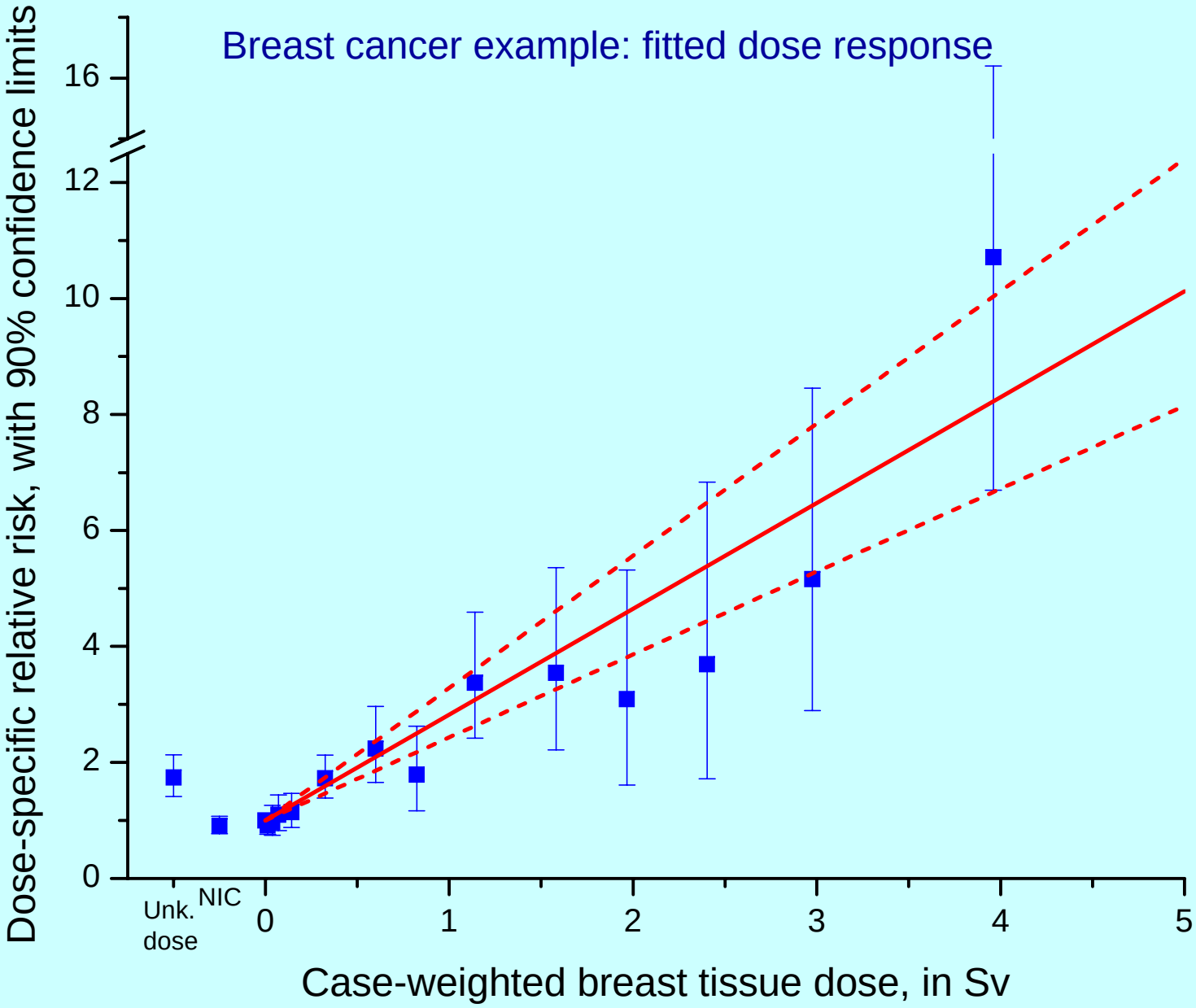
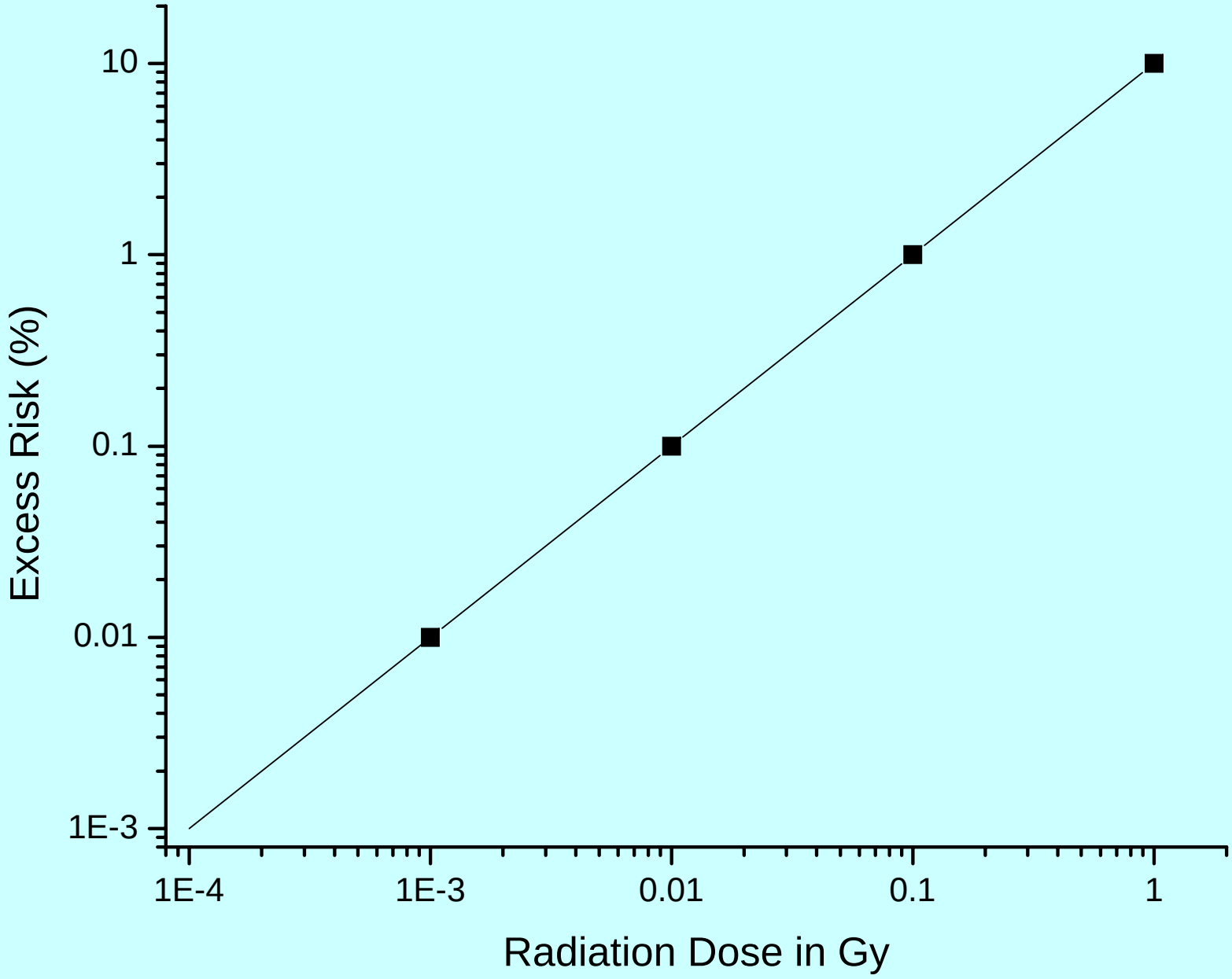
Introduction

- Ionizing radiation is a known, and well-quantified, human cancer risk factor
- But estimation of radiation-related cancer risk is uncertain
  - Statistical uncertainty
  - Transfer between populations
  - *Extrapolation to low doses*


Breast cancer example: fitted dose response
Dose-specific relative risk, with 90% confidence limits
16
12
10
8
6
4
2
0
Unk. dose
NIC
0
1
2
3
4
5
Case-weighted breast tissue dose, in Sv

An (overly) simple example

- Suppose a *known* population baseline cancer risk of 10% over a 30-year period (i.e., no need to estimate it)
- Suppose a uniform exposure, to dose D
- Suppose also that excess risk is proportional to dose, for $0 < D < 1$ Gy
- And that risk is doubled for $D = 1$ Gy
- For a 1-tailed test of size .05, how large a sample size, N, would be required for an 80% chance of detecting the radiation-related excess for different values of D?


10
1
0.1
0.01
1E-3
Excess Risk (%)
1E-4
1E-3
0.01
0.1
1
Radiation Dose in Gy

Example (cont.)

- Number of cancers is binomial (N, p), where p = 0.1 H (1+D)
- Estimated *excess* risk, E = (number of cancers) / N - 0.1, is approximately normally distributed with mean = 0.1 H D and variance = 0.1 H (1+D) H [1 - 0.1 H (1+D)] / N
- Under the null hypothesis of no excess, E has mean = 0 and variance = 0.09/N (standard deviation = 0.3/ $N^{½}$)
- Thus, we reject the null hypothesis if $N^{½}$H E / 0.3 > 1.645
- How large must N be for the probability of rejection to be $ 80%?

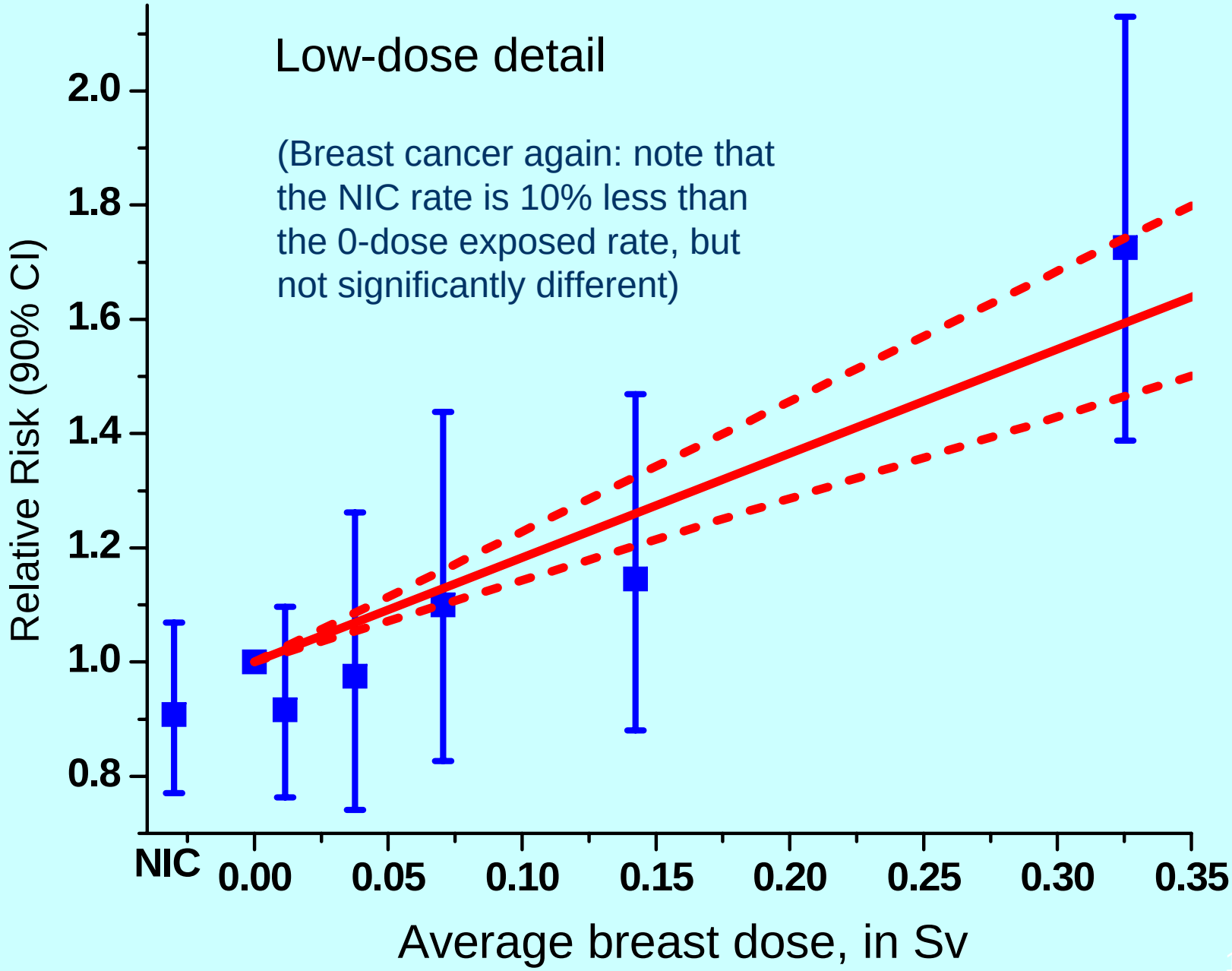
Dose D (Gy)	Excess Risk	Total Risk	$N^{1/2}$ × Standard Deviation of Estimate		Required Sample Size (N)
			Null Hypoth.	Alt. Hypoth.	
1.0	10%	20%	0.3	0.4	69
0.1	1%	11%	0.3	0.313	5728
0.01	0.1%	10.1%	0.3	0.301	558,000
0.001	0.01%	10.01%	0.3	0.300	55.7 million

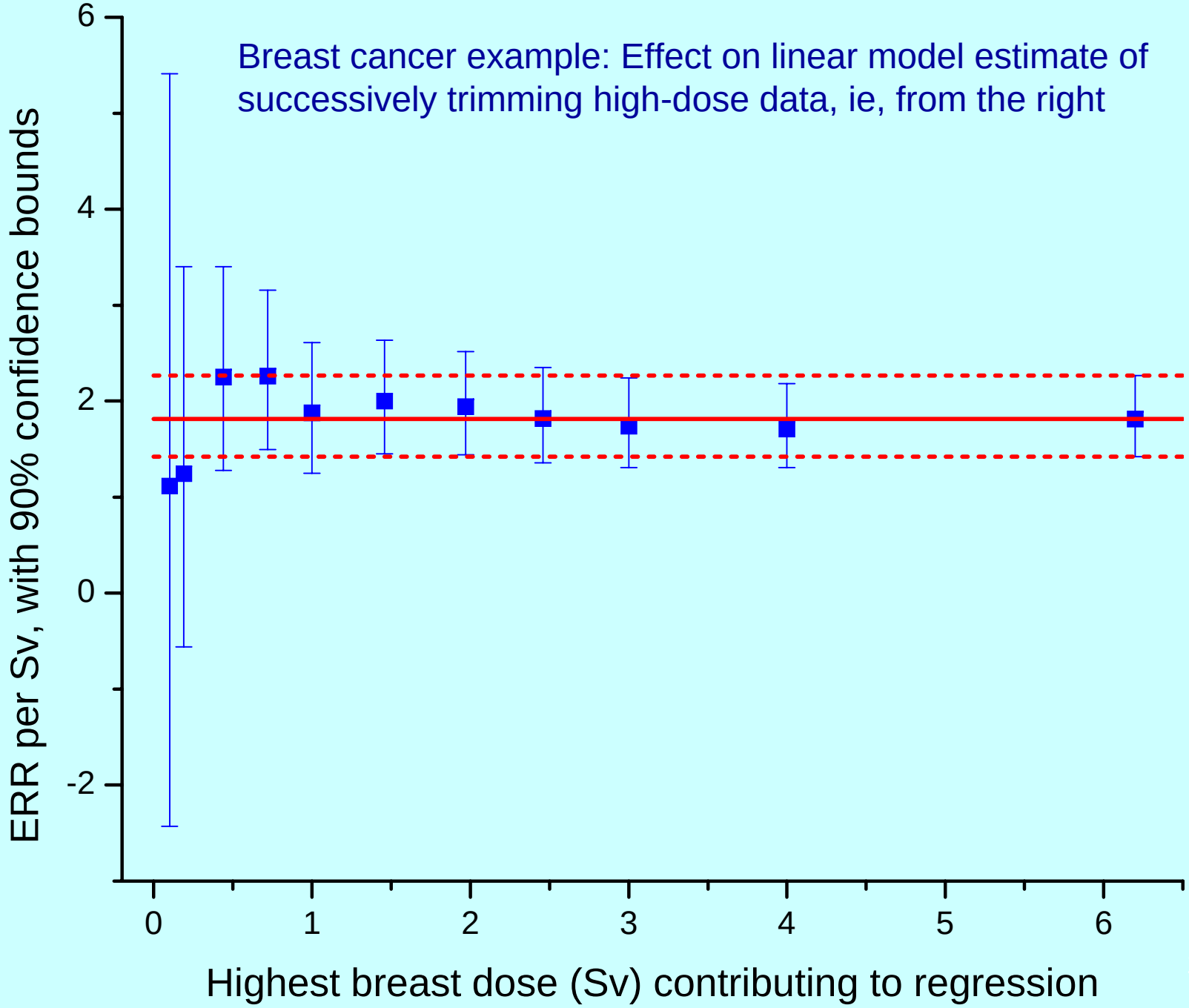
Example (cont)

- For D = 0.01 Gy (i.e., excess risk = 0.1%) and N = 50,000, the probability of rejecting the null hypothesis is .186
  - Under the null hypothesis, it is .05
  - Failure to reject would be predicted by both null and alternative hypotheses
- Thus, (in the example) even a large study would be very unlikely to yield conclusive results
  - In fact, a significant result would be misleading, because the estimated excess risk would be biased upward:
  - If the lower 95% confidence limit > 0 for N=50,000, estimate must be > 0.22%, over 2 times the true value

More bad news:

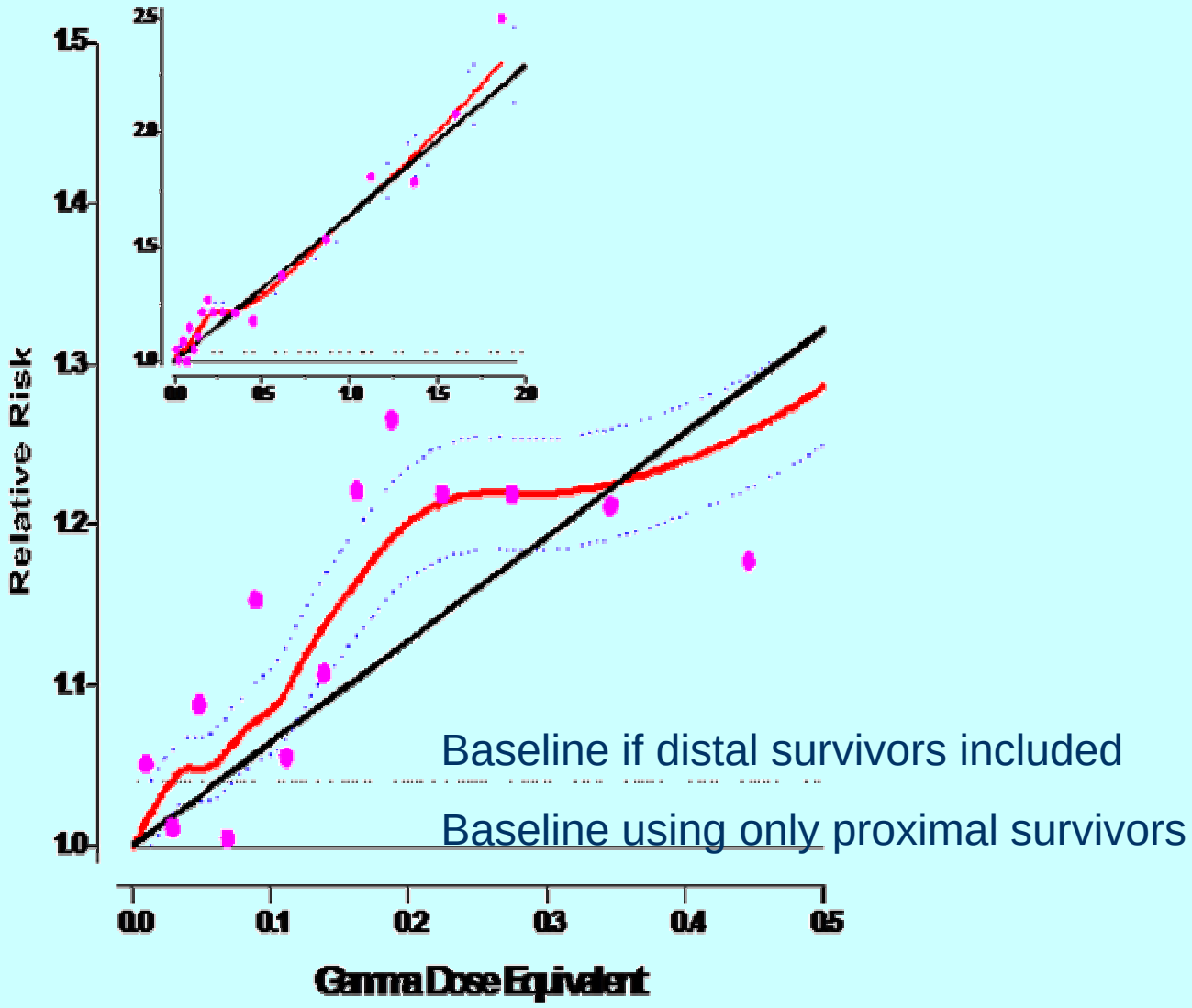
- In fact, sample size requirement is much more stringent
  - we don't "know" the baseline; we have to estimate it, which requires many more subjects
- And when we estimate the baseline,
  - Possibility of biased ascertainment of the baseline is serious when the predicted excess is low
  - How could we possibly control for every risk factor that might increase risk from 10% to 10.1%, or decrease it to 9.9%? How many such factors are known?
- Bottom line:
  - Stick to studies with reasonable power, judging by information from higher-dose studies
  - Low-dose extrapolation of estimates is unavoidable;
  - Direct estimation is likely to be either uninformative or misleading

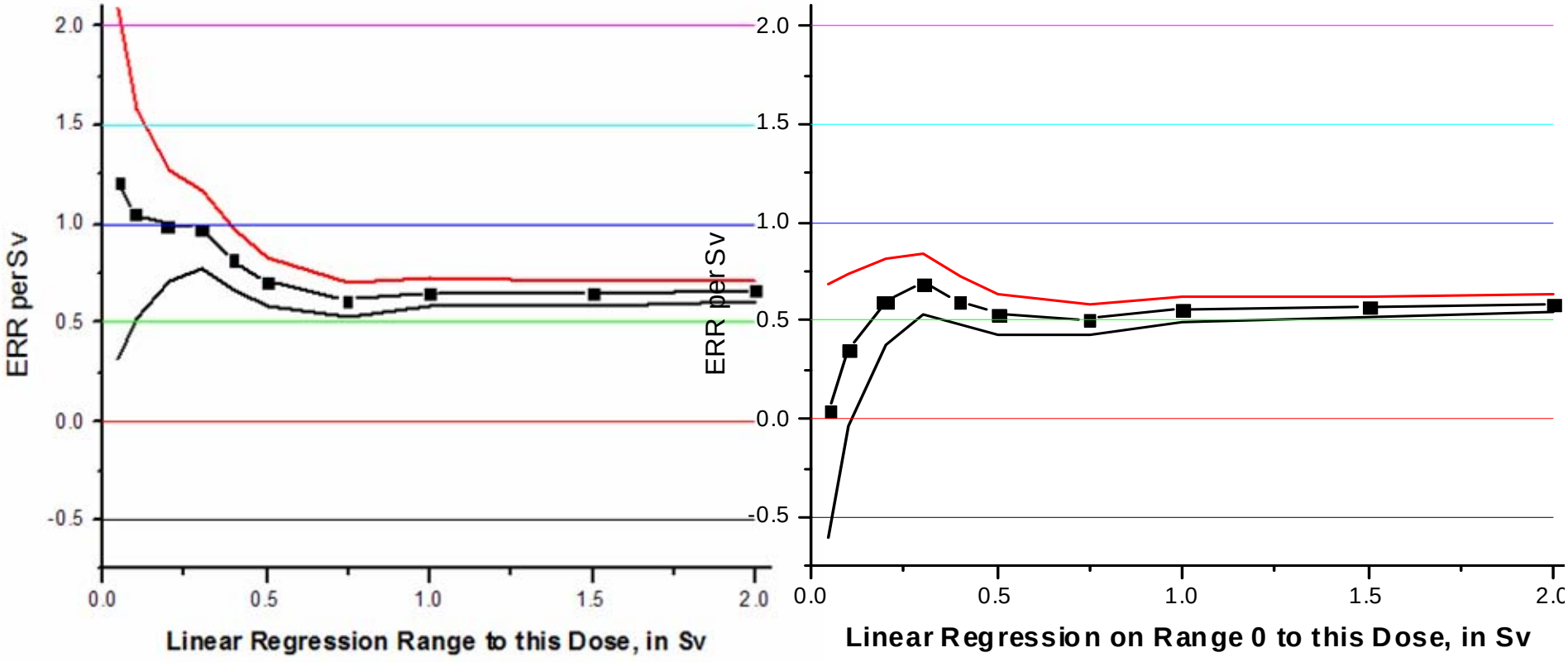

Low-dose detail
(Breast cancer again: note that the NIC rate is 10% less than the 0-dose exposed rate, but not significantly different)
Relative Risk (90% CI)
2.0
1.8
1.6
1.4
1.2
1.0
0.8
NIC
0.00
0.05
0.10
0.15
0.20
0.25
0.30
0.35
Average breast dose, in Sv


Breast cancer example: Effect on linear model estimate of successively trimming high-dose data, ie, from the right
ERR per Sv, with 90% confidence bounds
6
4
2
0
-2
0
1
2
3
4
5
6
Highest breast dose (Sv) contributing to regression

Pierce & Preston, Radiation Research, 2000; 154:178:86 (all solid cancers)

Note: error band is " 1 standard deviation





Linear regression estimates (" 1 s.d.) after trimming of high-dose data from the right.

Left-hand panel based on proximal (<3000m) survivors only; in right-hand panel the distal (>3000m) survivors also contribute, resulting in higher zero-dose baseline

Based on data of Pierce & Preston, Radiation Research, 2000; 154:178:86

The linear, no-threshold (LNT) model

- Currently, radiation protection philosophy is based on the LNT model
- The model states that, at low doses and low dose rates, excess risk is proportional to dose
- That doesn't require linearity of dose response over the entire dose range, just at low doses
- The ICRP posits a "dose and dose rate effectiveness factor" (DDREF) of 2 for low-LET radiation at low doses and dose rates for radiation protection
  - Where the DDREF applies, linear-model risk based on high-dose data is divided by it
  - In the example, excess risk at 10 mGy would be 0.05% instead of 0.1%
- A DDREF of 2 is implicit in the linear-quadratic model for leukemia

Implications of the LNT model

- If the estimated risk from 100 mGy to 10,000 people is 50 excess cancers,
  - The estimated risk from 10 mGy would be 5 excess cancers,
  - But the risk to 100,000 people would be 50 excess cancers
  - As would that for 1 mGy to 1,000,000 people
  - Or for 0.1 mGy to 10 million people
    - Of course, you'd never be able to prove it
    - It might be expensive to reduce the dose, and the 10 million people might not want to pay for it
    - They might feel that someone else should pay for it
    - But probably "someone else" would insist on proof

The low-dose threshold model

- If we could agree that there is no radiation-related cancer risk associated with doses below (say) 1 mGy, the 10 million people exposed to 0.1 mGy could relax
- Radiation protection would be cheaper and easier than it is today
- It would be even easier with a threshold at 10 mGy
- Unfortunately, a low-dose threshold at 10 mGy or 1 mGy would be difficult to prove, for the same reasons that make it difficult to demonstrate the opposite

A long-standing issue

- Source: Jennifer Caron, undergraduate thesis
  http://resolver.caltech.edu/CaltechETD:etd-03292004-111416
- Subject was leukemia risk associated with 90-Sr in global fallout from nuclear weapons testing during the 1950s & early 60s
  - Very small doses to very large populations
  - Leukemia risk had been demonstrated from higher-dose exposures:
    - A-bomb survivors, ankylosing spondylitis pts, thymic irrad pts, US radiologists
- Fruit fly geneticists found linear dose response for drosophila mutations down to 250 mGy
  - Also, the US radiologists' doses accumulated at rate of ~ 1 mGy per day; i.e., dose, and presumably risk, accumulated daily

Ed Lewis and Austin Brues

- Edward Lewis (1957) used available data on leukemia in radiation-exposed populations to fit a linear dose-response model
  - Argued for mutational factor in radiation leukemogenesis
  - Estimate: 2 excess leukemias per million per cGy per year
  - No experimental or epidemiological basis for radiation threshold
- Austin Brues, for AEC: toxicology model argues for radiation threshold – why should radiation be different?
  - Clearly there was a leukemia risk at high doses
  - But no direct proof of excess leukemia risk at very low doses
- The LNT model prevailed in radiation protection policy, but we are still in the same debate, and using many of the same arguments

Quick review of radiobiology

- Unique type of DNA damage by ionizing radiation involves multiple lesions in close proximity (clustered damage)
  - ~ 70% for high-LET, ~30% for low-LET
  - Can be induced by single electron track
  - Can compromise repair machinery
  - Processing and misrepair can lead to chromosome aberrations and mutation
    - i.e., damaged or altered cells can escape cell cycle checkpoint and apoptotic pathways
- Roles of radiation-related adaptive response, genomic instability, & bystander effects not well understood; may not be relevant to threshold question
- Critical radiation events in tumorigenic process are mostly early events involving DNA losses and critical genes
- Mechanistic arguments support linear response in low-dose region

Evidence differs by tissue

- Stem cells in the intestinal crypt of laboratory mouse: Selective retention of template DNA strands in stem cells, providing protection of the stem cell genome (Cairns 1975; 2002)
- But induction of small intestine cancer by high-dose radiation of exteriorized loop is a well-established experimental procedure
- Very different for colon, for which there is clearly a low-dose risk

Epidemiological evidence re: threshold

- For:
  - Shape of dose responses for basal cell skin carcinoma, bone, soft tissue sarcoma, rectum, small intestine
  - Apparent fractionation effect for lung cancer
- Against:
  - X-ray pelvimetry studies (leukemia, solid cancers)
  - TB, scoliosis fluoroscopy studies (female breast)
  - Linear dose responses for female breast, thyroid, all solid cancers combined

- Experimental and epidemiological evidence doesn’t preclude tissue-specific thresholds
- But it doesn’t support existence of a universal threshold, operating in all tissues
- And a threshold has to be universal to have much influence on radiation protection policy

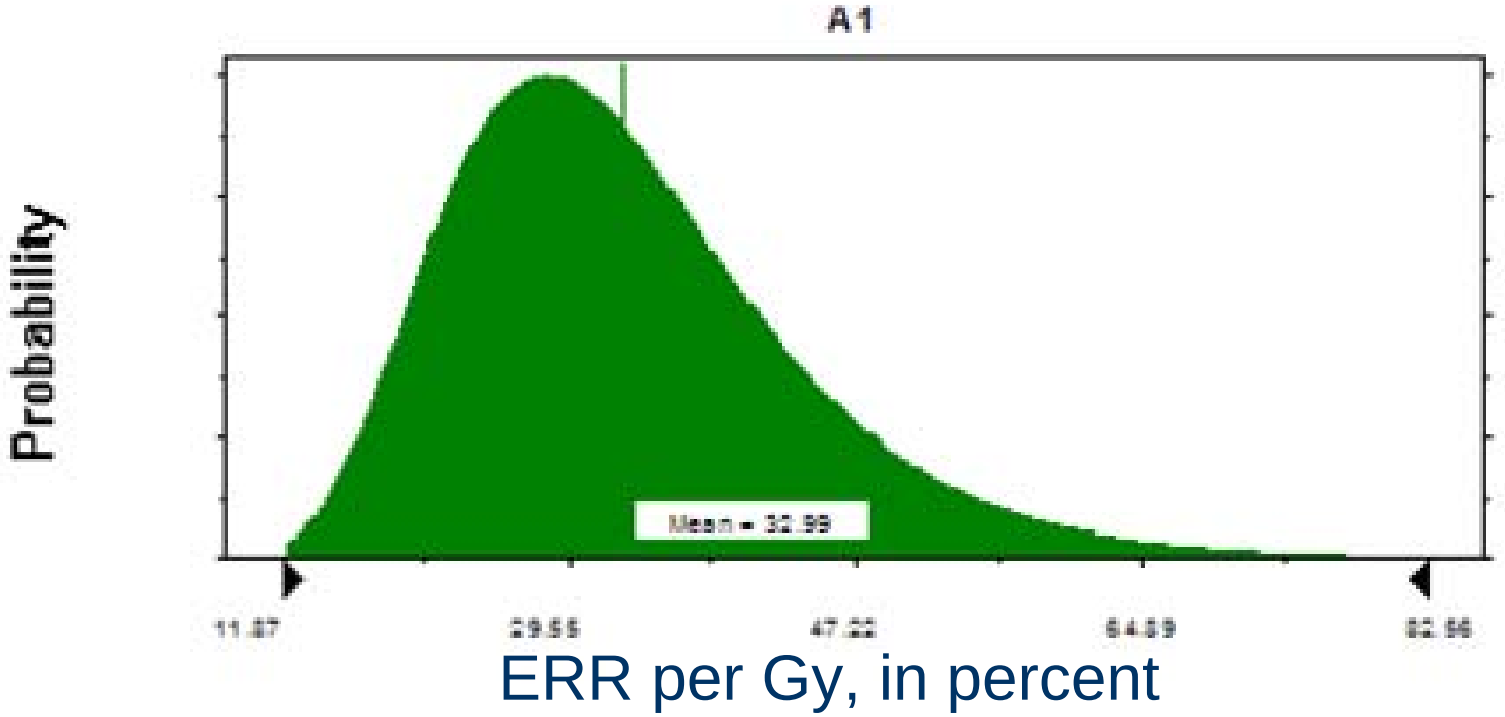
Quantitative Uncertainty Analysis

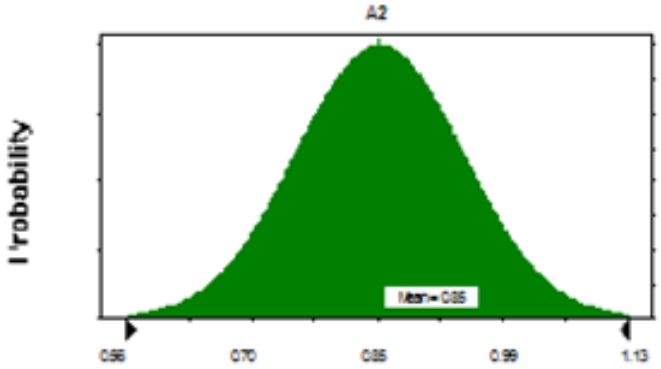
- Method much used in risk analysis
- Has advantage of transparency
- For it to be persuasive, audience has to understand how it works:
  - Identify components of risk estimation process
  - Determine uncertainties of each, and propagate the uncertainties by examining how the components interact
  - Evaluate the uncertainty of the risk estimate

Major uncertain components

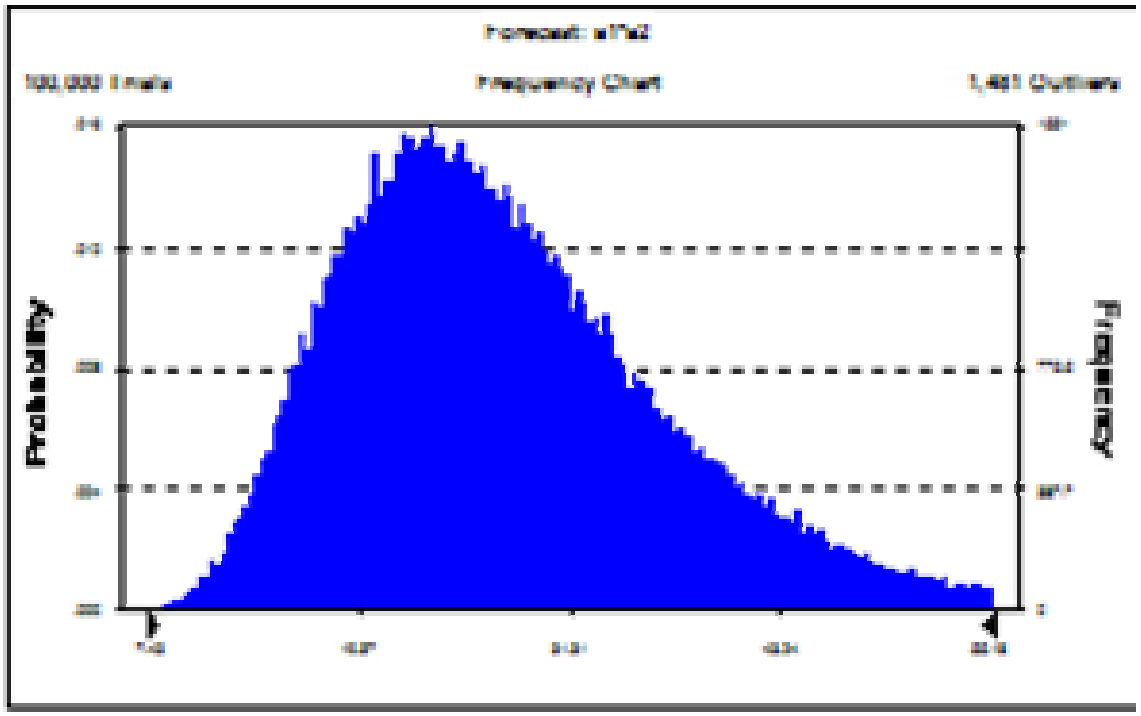
- Linear model estimate of ERR at 1Gy
  - Statistical likelihood contour
- Correction for DS86-related bias
- Correction for transfer from LSS to US population
- DDREF to be applied at low doses and low dose rates
- Possibility of a universal threshold at some dose above that of interest

Lognormal statistical uncertainty distribution for all solid cancers, LSS population. Sex-averaged ERR per Gy at age 50 following exposure at age 30. Mean 0.33, 90% uncertainty limits 0.18 and 0.43. Obtained from likelihood contour.

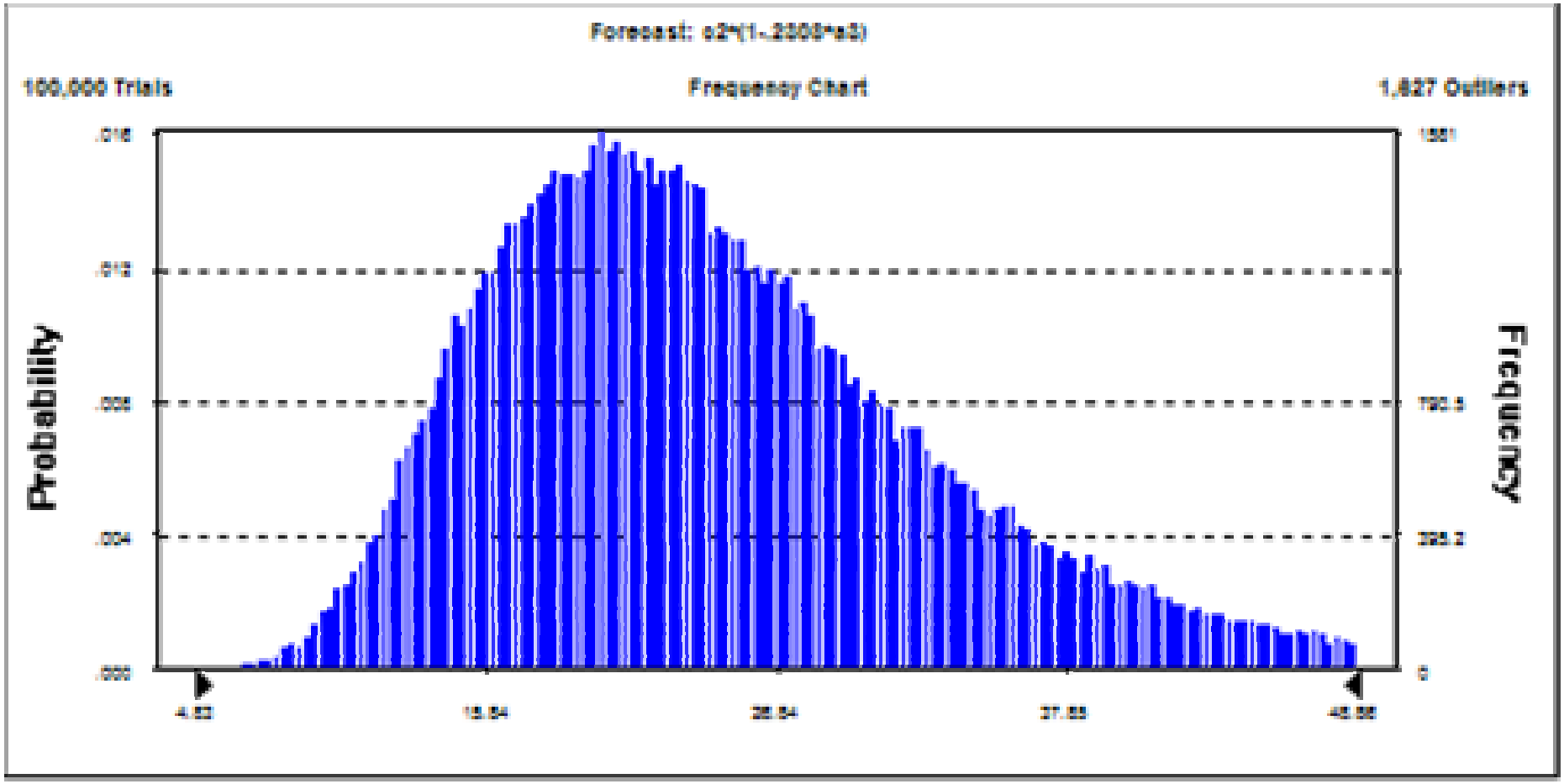




Normal uncertainty distribution for dosimetry bias correction factor, with mean 0.84 and 90% uncertainty limits 0.69-1.0. (From NCRP Rept. 126)



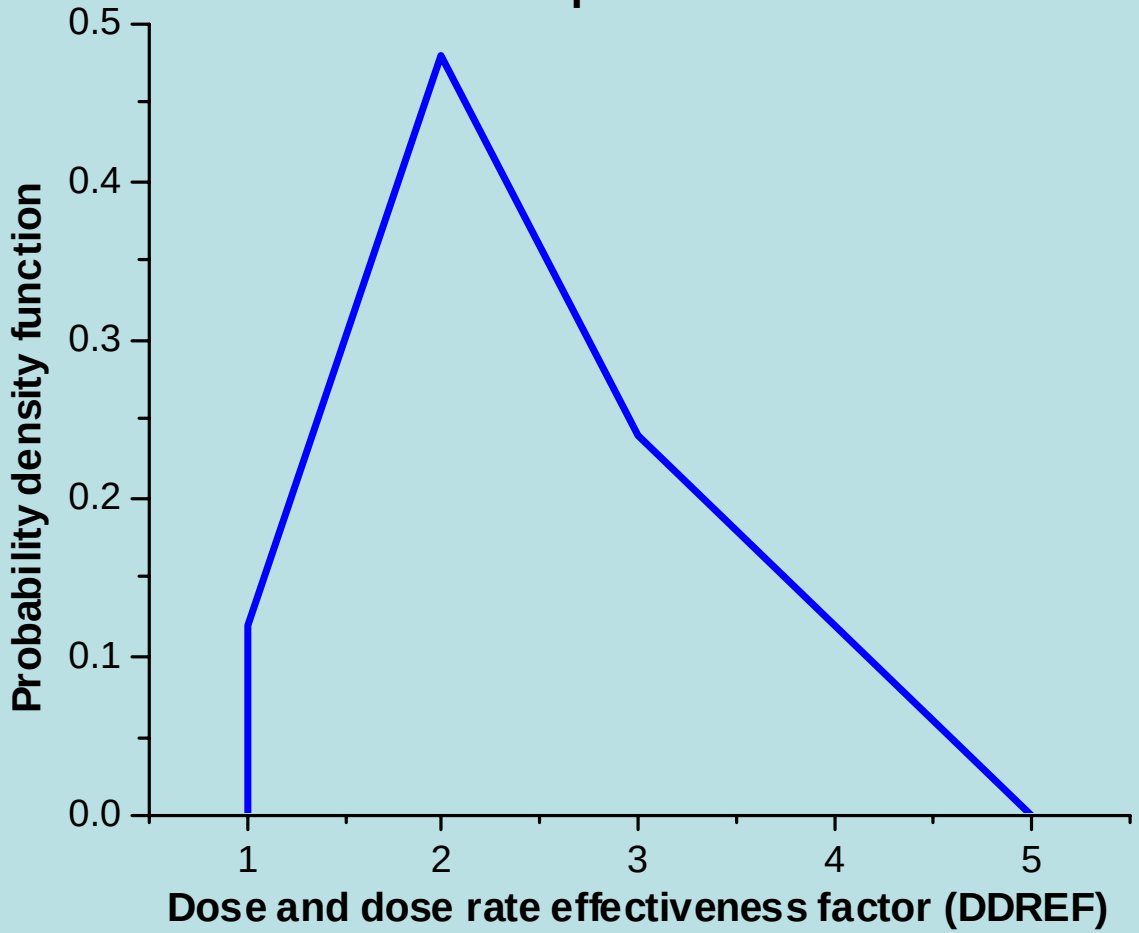
Approximately lognormal, corrected uncertainty distribution for ERR per Gy, with mean 0.26 and 90% uncertainty limits 0.15-0.46.

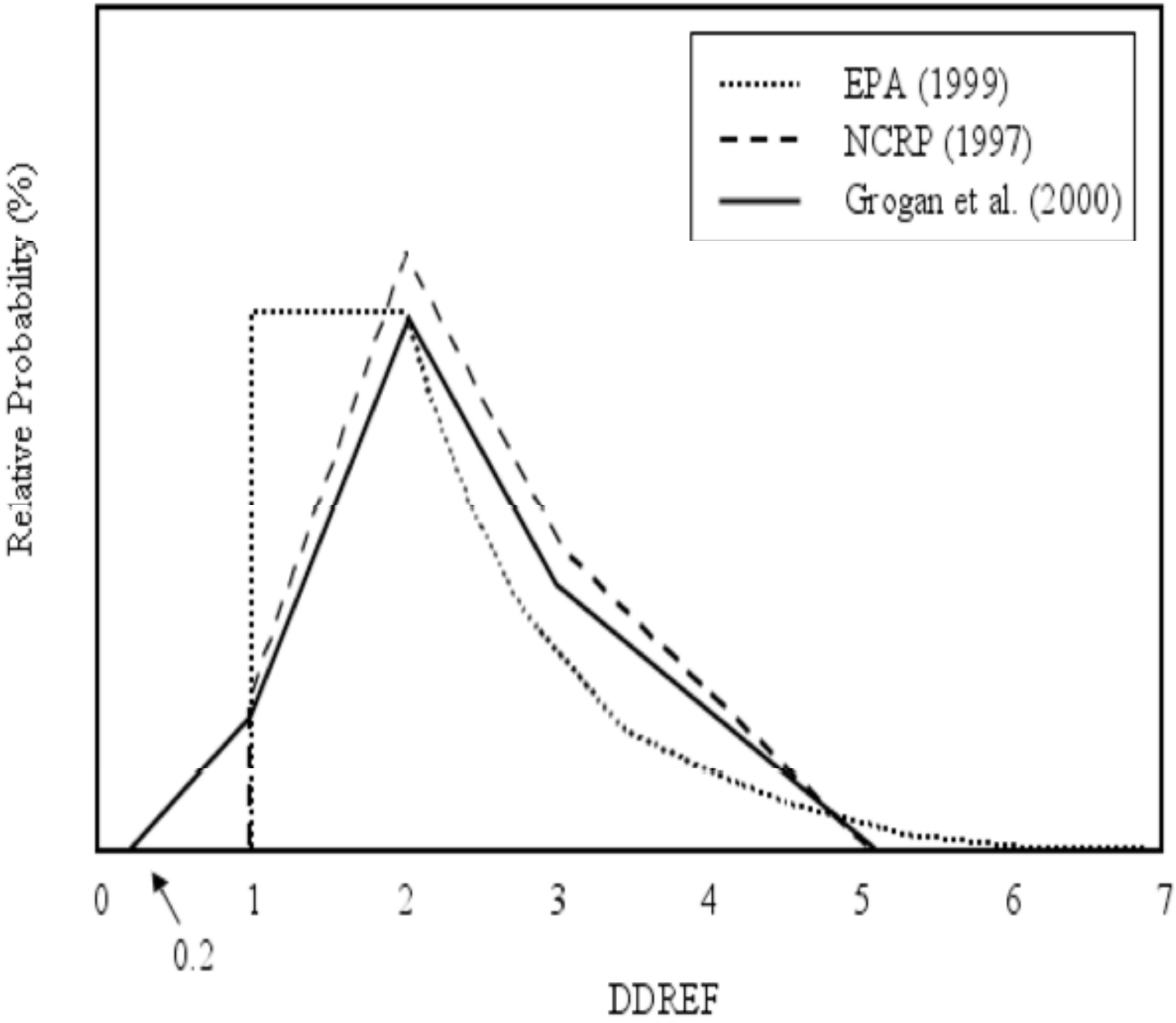


Monte Carlo simulation of the uncertainty distribution for cancer ERR at 1 Sv, after transfer to a U.S. population: the simulated distribution is approximately lognormal with mean 0.25 and 90% probability limits 0.13 – 0.41.

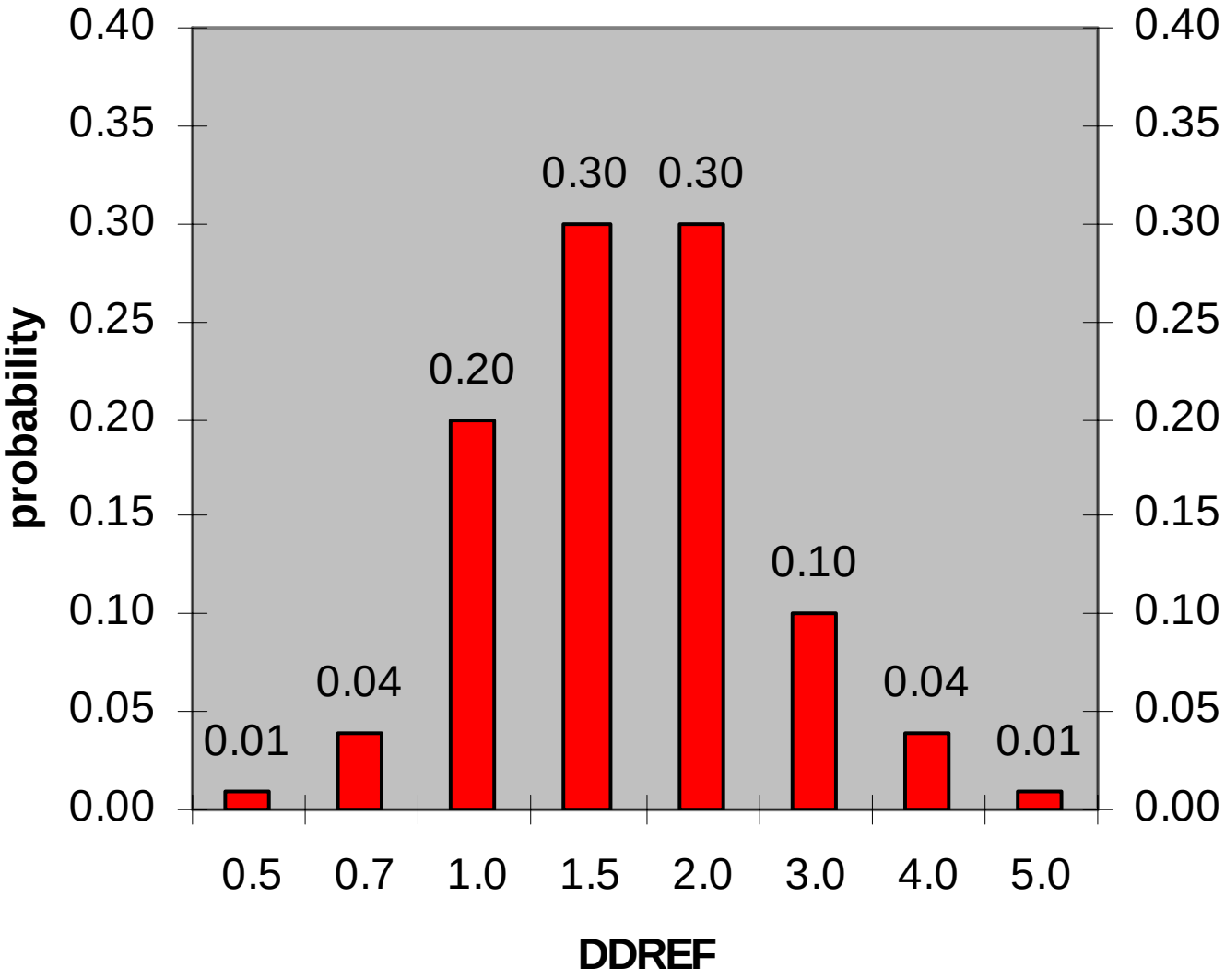
NCRP 126 Uncertainty Model for DDREF:

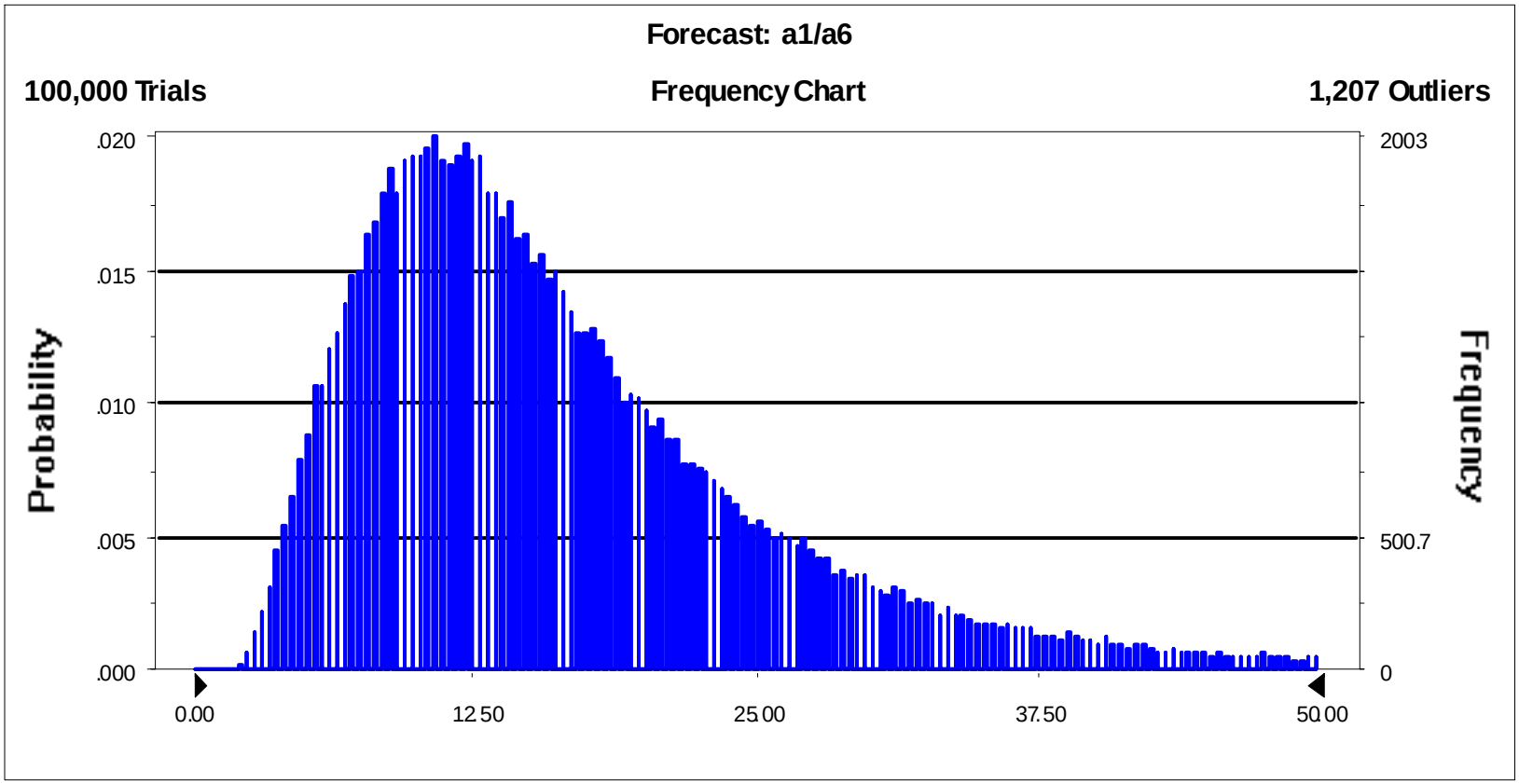
Figure 5. Subjective uncertainty of DDRF factor for low-dose extrapolation of risk.




EPA (1999)
NCRP (1997)
Grogan et al. (2000)
Relative Probability (%)
0
0.2
1
2
3
4
5
6
7
DDREF

DDREF for solid tumors other than breast and thyroid





Monte Carlo simulation of the uncertainty distribution for low-dose cancer ERR per Sv, after division by an uncertain DDREF: the simulated distribution is roughly lognormal with mean 0.17 and 90% probability limits 0.08 – 0.36.

Point of view:

Implications of an uncertain risk estimate

- It is widely recognized that risk estimation is uncertain
  - Uncertainty distributions like the one in the previous slide aren't a new idea
- Formally, radiation protection today is based on a single, central value, e.g., the mean
- But it is not immune from political considerations

Point of view (cont.)

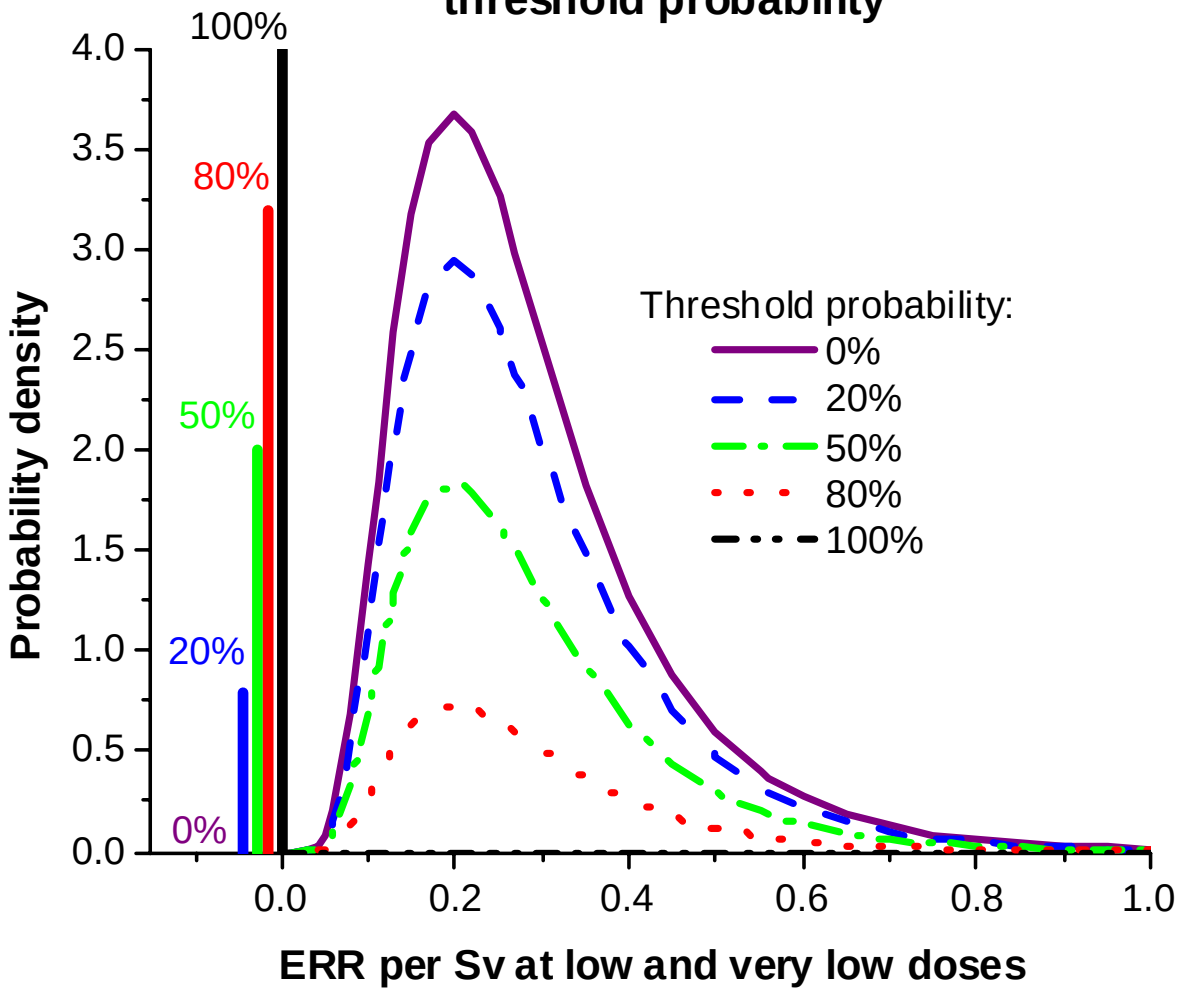
- The uncertainty distribution summarizes all the identified information about risk
  - But we can't think of everything
- The exposed population presumably is concerned with upper limits on risk
  - How bad might it be? Is the benefit really worth the risk?
- Those liable for the expense of dose reduction tend to be more concerned with lower limits
  - Is there strong statistical evidence that there is a risk, or that the risk high enough to be of concern? (Can you prove it?)
- Sometimes those exposed and those liable for the expense are the same – e.g., radiation workers

Uncertain possibility of a threshold

- Consider a threshold somewhere above (say) 1 mGy as an uncertain possibility, with probability *p.*
- Then, with probability *p*, ERR at 1 mGy would be zero
- And with probability *1-p*, ERR at 1 mGy would be an uncertain quantity, distributed lognormally with mean 0.17 H 0.001 and upper 95% probability limit 0.36 H 0.001

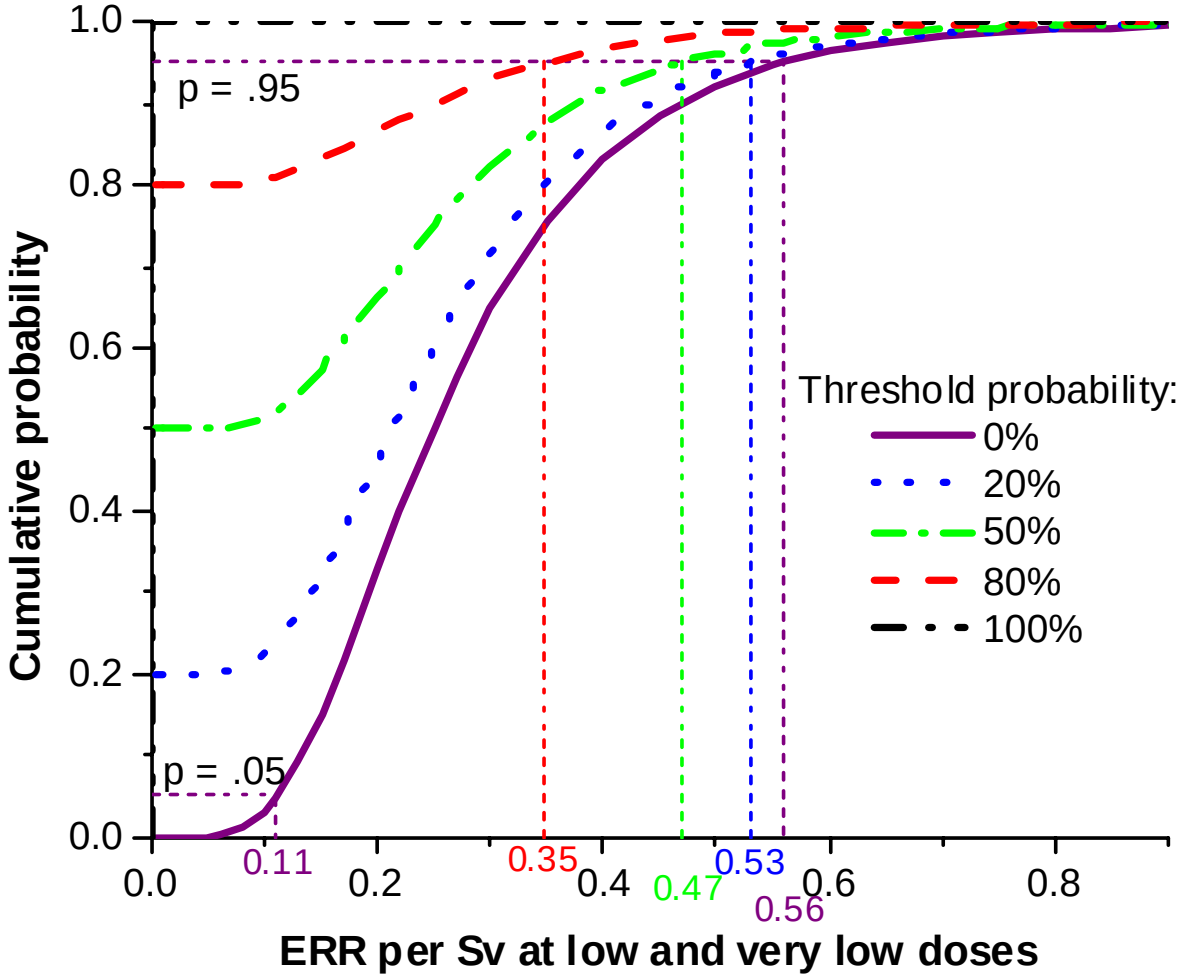
Uncertain possibility of a threshold

Figure 8. Credibility distributions for low-dose risk, by assumed threshold probability



Uncertain threshold possibility

Figure 9. Influence of assumed threshold probability on upper (and lower) 95% credibility limits for low-dose risk

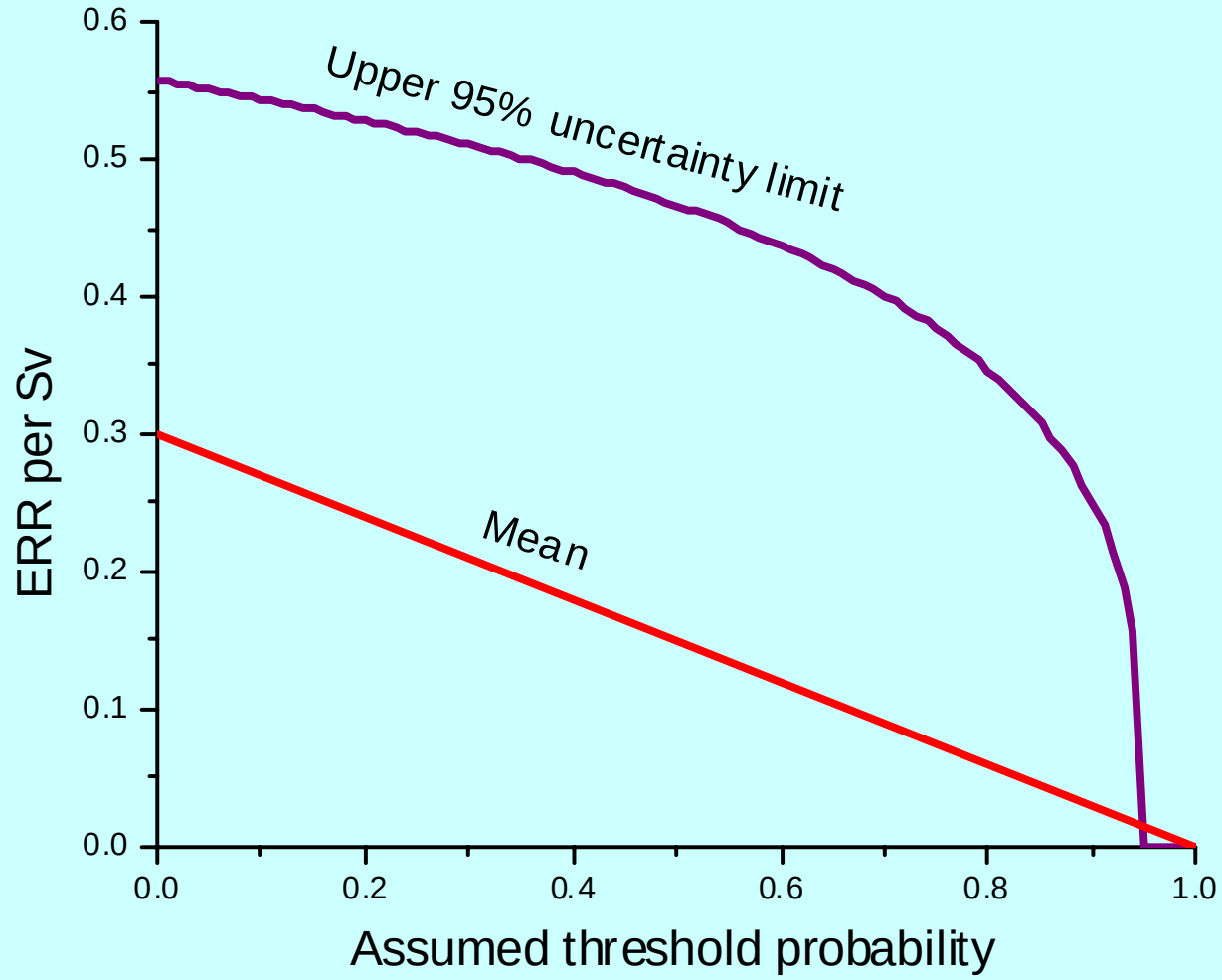


Assume uncertain threshold possibility, with probability *p*

- QUA approach: risk at 1 mSv is
  - zero with probability *p*
  - lognormal (0.025%, 1.64) with probability *1-p*

p	mean	95% upper limit
0	0.03%	0.056%
0.2	0.024%	0.053%
0.5	0.015%	0.047%
0.8	0.006%	0.035%
1	0	0

Effect of uncertain threshold assumption on a lognormal (GM 0.25, GSD 1.64) uncertainty distribution for ERR per Sv



Implications of an uncertain threshold for radiation protection

- For the simple case (threshold probability = *p*)
  - The mean of the uncertainty distribution for excess risk is multiplied by *1-p* and therefore decreases with increasing *p*
  - An upper uncertainty limit also decreases with increasing *p*, but the decrease is rather slow until *p* approaches 1.
- The epidemiological and radiobiological information available does not suggest a high value for *p* at any dose level high enough to matter.
- Thus, allowing for the *possibility* of a threshold would make very little difference to radiation protection